


Reglan® Tablets
(Metoclopramide Tablets, USP)
Reglan® Syrup
(Metoclopramide Oral Solution, USP)
Reglan® Injectable
(Metoclopramide Injection, USP)
CI 6015-3

 only

DESCRIPTION

For oral administration, Reglan Tablets (Metoclopramide Tablets, USP) 10 mg are white, scored, capsule-shaped tablets engraved Reglan on one side and AHR 10 on the opposite side.

Each tablet contains:
Metoclopramide base10 mg
(as the monohydrochloride monohydrate)

Inactive Ingredients
Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Stearic Acid.

Reglan Tablets (Metoclopramide Tablets, USP) 5 mg are green, elliptical-shaped tablets engraved Reglan 5 on one side and AHR on the opposite side.

Each tablet contains:
Metoclopramide base5 mg
(as the monohydrochloride monohydrate)

Inactive Ingredients
Corn Starch, D&C Yellow 10 Lake, FD&C Blue 1 Aluminum Lake, Lactose, Microcrystalline Cellulose, Silicon Dioxide, Stearic Acid.

Reglan Syrup (Metoclopramide Oral Solution, USP) is an orange-colored, palatable, aromatic, sugar-free liquid.

Each 5 mL (1 teaspoonful) contains:
Metoclopramide base5 mg
(as the monohydrochloride monohydrate)

Inactive Ingredients:
Citric Acid, FD&C Yellow 6, Flavors, Glycerin, Methylparaben, Propylparaben, Sorbitol, Water.

For parenteral administration, Reglan Injectable (Metoclopramide Injection, USP) is a clear, colorless, sterile solution with a pH of 4.5-6.5 for intravenous or intramuscular administration.

CONTAINS NO PRESERVATIVE.

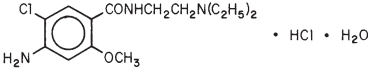
This product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

2 mL single dose vials/ampuls; 10 mL and 30 mL single dose vials

Each 1 mL contains:
Metoclopramide base5 mg
(as the monohydrochloride monohydrate)

Sodium Chloride, USP 8.5 mg, Water for Injection, USP q.s. pH adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide.

Metoclopramide hydrochloride is a white crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide mono-hydrochloride monohydrate. Its molecular formula is C₁₄H₂₂ClN₃O₂•HCl•H₂O. Its molecular weight is 354.3.



CLINICAL PHARMACOLOGY

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any, effect on the motility of the colon or gallbladder.

In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5 mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like l-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions, although these are comparatively rare (see **WARNINGS**). Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with transient fluid retention.

The onset of pharmacological action of metoclopramide is 1 to 3 minutes following an intravenous dose, 10 to 15 minutes following intramuscular administration, and 30 to 60 minutes following an oral dose; pharmacological effects persist for 1 to 2 hours.

Pharmacokinetics

Metoclopramide is rapidly and well absorbed. Relative to an intravenous dose of 20 mg, the absolute oral bioavailability of metoclopramide is 80% ± 15.5% as demonstrated in a crossover study of 18 subjects. Peak plasma concentrations occur at about 1-2 hr after a single oral dose. Similar time to peak is observed after individual doses at steady state.

In a single dose study of 12 subjects, the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5-6 hr. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hr. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide.

The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to the tissues.

Renal impairment affects the clearance of metoclopramide. In a study with patients with varying degrees of renal impairment, a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance, and increase in elimination half-life. The kinetics of metoclopramide in the presence of renal impairment remained linear however. The reduction in clearance as a result of renal impairment suggests that adjustment downward of maintenance dosage should be done to avoid drug accumulation.

Adult Pharmacokinetic Data		
Parameter	Value	
Vd (L/kg)	~ 3.5	
Plasma Protein Binding	~ 30%	
t _{1/2} (hr)	5-6	
Oral Bioavailability	80%±15.5%	

In pediatric patients, the pharmacodynamics of metoclopramide following oral and intravenous administration are highly variable and a concentration-effect relationship has not been established.

There are insufficient reliable data to conclude whether the pharmacokinetics of metoclopramide in adults and the pediatric population are similar.

Although there are insufficient data to support the efficacy of metoclopramide in pediatric patients with symptomatic gastroesophageal reflux (GER) or cancer chemotherapy-related nausea and vomiting, its pharmacokinetics have been studied in these patient populations.

In an open-label study, six pediatric patients (age range, 3.5 weeks to 5.4 months) with GER received metoclopramide 0.15 mg/kg oral solution every 6 hours for 10 doses. The mean peak plasma concentration of metoclopramide after the tenth dose was 2-fold (56.8 µg/L) higher compared to that observed after the first dose (29 µg/L) indicating drug accumulation with repeated dosing. After the tenth dose, the mean time to reach peak concentrations (2.2 hr), half-life (4.1 hr), clearance (0.67 L/h/kg), and volume of distribution (4.4 L/kg) of metoclopramide were similar to those observed after the first dose. In the youngest patient (age, 3.5 weeks), metoclopramide half-life after the first and the tenth dose (23.1 and 10.3 hr, respectively) was significantly longer compared to other infants due to reduced clearance. This may be attributed to immature hepatic and renal systems at birth.

Single intravenous doses of metoclopramide 0.22 to 0.46 mg/kg (mean, 0.35 mg/kg) were administered over 5 minutes to 9 pediatric cancer patients receiving chemotherapy (mean age, 11.7 years; range, 7 to 14 yr) for prophylaxis of cytotoxic-induced vomiting. The metoclopramide plasma concentrations extrapolated to time zero ranged from 65 to 395 µg/L (mean, 152 µg/L). The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.4 hr (range, 1.7 to 8.3 hr), 0.56 L/h/kg (range, 0.12 to 1.20 L/h/kg), and 3.0 L/kg (range, 1.0 to 4.8 L/kg), respectively.

In another study, nine pediatric cancer patients (age range, 1 to 9 yr) received 4 to 5 intravenous infusions (over 30 minutes) of metoclopramide at a dose of 2 mg/kg to control emesis. After the last dose, the peak serum concentrations of metoclopramide ranged from 1060 to 5680 µg/L. The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.5 hr (range, 2.0 to 12.5 hr), 0.37 L/h/kg (range, 0.10 to 1.24 L/h/kg), and 1.93 L/kg (range, 0.95 to 5.50 L/kg), respectively.

Pediatric Pharmacokinetic Studies					
Reference	Dose, Route	t _{1/2} (hr)	Cl (L/hr/kg)	Vd (L/kg)	Cmax (µg/L)
1.	0.15 mg/kg oral soln, multiple dose	4.1 ^{a,b}	0.67±0.14	4.4±0.65 (Vd _{area})	1st dose = 29±2.3 10th dose = 56.8±10.5
2.	0.35 mg/kg, IV over 5 min	4.4±0.56	0.56±0.10	3.0±0.38 (Dose/Cp ⁰)	152±31
3.	2 mg/kg 30 min IV infusion 4-5 times within 9.5 hours	4.5 ^b	0.37 ^b	1.93 ^b	1060 to 5680 ^b

^a. Data presented as means ± SEM.
^b. SEM not available.

1. Kearns, GL, et al. *J Pediatric Gastroenterol Nutr* 7(6):823-829, 1988.

2. Bateman, DN, et al. *Br J Clin Pharmac* 15:557-559, 1983.

3. Ford, C. *Clin Pharmac Ther* 43:196, 1988.

INDICATIONS AND USAGE

Symptomatic Gastroesophageal Reflux

Reglan Tablets and Syrup are indicated as short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy. The principal effect of metoclopramide is on symptoms of postprandial and daytime heartburn with less observed effect on nocturnal symptoms. If symptoms are confined to particular situations, such as following the evening meal, use of metoclopramide as single doses prior to the provocative situation should be considered, rather than using the drug throughout the day. Healing of esophageal ulcers and erosions has been endoscopically demonstrated at the end of a 12-week trial using doses of 15 mg q.i.d. As there is no documented correlation between symptoms and healing of esophageal lesions, patients with documented lesions should be monitored endoscopically.

Diabetic Gastroparesis (Diabetic Gastric Stasis)

Reglan (Metoclopramide Hydrochloride, USP) is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartburn, persistent fullness after meals, and anorexia) appear to respond to Reglan within different time intervals. Significant relief of nausea occurs early and continues to improve over a three-week period. Relief of vomiting and anorexia may precede the relief of abdominal fullness by one week or more.

The Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy

Reglan Injectable is indicated for the prophylaxis of vomiting associated with emetogenic cancer chemotherapy.

The Prevention of Postoperative Nausea and Vomiting

Reglan Injectable is indicated for the prophylaxis of postoperative nausea and vomiting in those circumstances where nasogastric suction is undesirable.

Small Bowel Intubation

Reglan Injectable may be used to facilitate small bowel intubation in adults and pediatric patients in whom the tube does not pass the pylorus with conventional maneuvers.

Radiological Examination

Reglan Injectable may be used to stimulate gastric emptying and intestinal transit of barium in cases where delayed emptying interferes with radiological examination of the stomach and/or small intestine.

CONTRAINDICATIONS

Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine.

Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug.

Metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.

WARNINGS

Mental depression has occurred in patients with and without prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the usual adult dosages of 30-40 mg/day of metoclopramide. These usually are seen during the first 24-48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and adult patients less than 30 years of age and are even more frequent at the higher doses used in prophylaxis of vomiting due to cancer chemotherapy. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, or dystonic reactions resembling tetanus. Rarely, dystonic reactions may present as stridor and dyspnea, possibly due to laryngospasm. If these symptoms should occur, inject 50 mg Benadryl® (diphenhydramine hydrochloride) intramuscularly, and they usually will subside. Cogentin® (benztropine mesylate), 1 to 2 mg intramuscularly, may also be used to reverse these reactions. Parkinsonian-like symptoms have occurred, more commonly within the first 6 months after beginning treatment with metoclopramide, but occasionally after longer periods. These symptoms generally subside within 2-3 months following discontinuance of metoclopramide. Patients with preexisting Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible.

There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.

Neuroleptic Malignant Syndrome

There have been rare reports of an uncommon but potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) associated with metoclopromide. Clinical manifestations of NMS include hyperthermia, muscle rigidity, altered consciousness, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac arrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, malignant hyperthermia, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of metoclopromide and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. Bromocriptine and dantroline sodium have been used in treatment of NMS, but their effectiveness have not been established (see **ADVERSE REACTIONS**).

PRECAUTIONS

General

In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; hence, caution should be exercised when metoclopramide is used in patients with hypertension.

Intravenous injections of undiluted metoclopramide should be made slowly allowing 1 to 2 minutes for 10 mg since a transient but intense feeling of anxiety and restlessness, followed by drowsiness, may occur with rapid administration.

Because metoclopramide produces a transient increase in plasma aldosterone, certain patients, especially those with cirrhosis or congestive heart failure, may be at risk of developing fluid retention and volume overload. If this occurs within the first few weeks of metoclopramide therapy, the drug should be discontinued.

Intravenous administration of Reglan Injectable diluted in a parenteral solution should be made slowly over a period of not less than 15 minutes.

Giving a promotility drug such as metoclopramide theoretically could put increased pressure on suture lines following a gut anastomosis or closure. This possibility should be considered and weighed when deciding whether to use metoclopramide or nasogastric suction in the prevention of postoperative nausea and vomiting.

Information for Patients

Metoclopramide may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be cautioned accordingly.

Drug Interactions

The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers. The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

Absorption of drugs from the stomach may be diminished (e.g., digoxin) by metoclopramide, whereas the rate and/or extent of absorption of drugs from the small bowel may be increased (e.g., acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

Gastroparesis (gastric stasis) may be responsible for poor diabetic control in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because the action of metoclopramide will influence the delivery of food to the intestines and thus the rate of absorption, insulin dosage or timing of dosage may require adjustment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 77-week study was conducted in rats with oral doses up to about 40 times the maximum recommended human daily dose. Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

An Ames mutagenicity test performed on metoclopramide was negative.

Pregnancy Category B

Reproduction studies performed in rats, mice and rabbits by the I.V., I.M., S.C., and oral routes at maximum levels ranging from 12 to 250 times the human dose have demonstrated no impairment of fertility or significant harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established except as stated to facilitate small bowel intubation (see **OVERDOSAGE** and **DOSAGE AND ADMINISTRATION**).

Care should be exercised in administering metoclopramide to neonates since prolonged clearance may produce excessive serum concentrations (see **CLINICAL PHARMACOLOGY—Pharmacokinetics**). In addition, neonates have reduced levels of nicotinamide adenine dinucleotide-methemoglobin reductase which, in combination with the aforementioned pharmacokinetic factors, make neonates more susceptible to methemoglobinemia (see **OVERDOSAGE**).

The safety profile of metoclopramide in adults cannot be extrapolated to pediatric patients. Dystonias and other extrapyramidal reactions associated with metoclopramide are more common in the pediatric population than in adults. (See **WARNINGS** and **ADVERSE REACTIONS—Extrapyramidal Reactions**.)

ADVERSE REACTIONS

In general, the incidence of adverse reactions correlates with the dose and duration of metoclopramide administration. The following reactions have been reported, although in most instances, data do not permit an estimate of frequency:

CNS Effects

Restlessness, drowsiness, fatigue, and lassitude occur in approximately 10% of patients receiving the most commonly prescribed dosage of 10 mg q.i.d. (see **PRECAUTIONS**). Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation (see **WARNINGS**) occur less frequently. In cancer chemotherapy patients being treated with 1-2 mg/kg per dose, incidence of drowsiness is about 70%. There are isolated reports of convulsive seizures without clearcut relationship to metoclopramide. Rarely, hallucinations have been reported.

Extrapyramidal Reactions (EPS)

Acute dystonic reactions, the most common type of EPS associated with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30 to 40 mg of metoclopramide per day. In cancer chemotherapy patients receiving 1-2 mg/kg per dose, the incidence is 2% in patients over the ages of 30-35, and 25% or higher in pediatric patients and adult patients less than 30 years of age who have not had prophylactic administration of diphenhydramine. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (tetanus-like reactions), and, rarely, stridor and dyspnea possibly due to laryngospasm; ordinarily these symptoms are readily reversed by diphenhydramine (see **WARNINGS**).

Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, mask-like facies (see **WARNINGS**).

Tardive dyskinesia most frequently is characterized by involuntary movements of the tongue, face, mouth, or jaw, and sometimes by involuntary movements of the trunk and/or extremities; movements may be choreoathetotic in appearance (see **WARNINGS**).

Motor restlessness (akathisia) may consist of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing, foot tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

Neuroleptic Malignant Syndrome

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported. This potentially fatal syndrome is comprised of the symptom complex of hyperthermia, altered consciousness, muscular rigidity, and autonomic dysfunction (see **WARNINGS**).

Endocrine Disturbances

Galactorrhea, amenorrhea, gynecomastia, impotence secondary to hyperprolactinemia (see **PRECAUTIONS**). Fluid retention secondary to transient elevation of aldosterone (see **CLINICAL PHARMACOLOGY**).

Cardiovascular

Hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention, acute congestive heart failure and possible AV block (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Gastrointestinal

Nausea and bowel disturbances, primarily diarrhea.

Hepatic

Rarely, cases of hepatotoxicity, characterized by such findings as jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

Renal

Urinary frequency and incontinence.

Hematologic

A few cases of neutropenia, leukopenia, or agranulocytosis, generally without clearcut relationship to metoclopramide. Methemoglobinemia, especially with overdosage in neonates (see **OVERDOSAGE**). Sulfhemoglobinemia in adults.

Allergic Reactions

A few cases of rash, urticaria, or bronchospasm, especially in patients with a history of asthma. Rarely, angioneurotic edema, including glossal or laryngeal edema.

Miscellaneous

Visual disturbances. Porphyria.

Transient flushing of the face and upper body, without alterations in vital signs, following high doses intravenously.

OVERDOSAGE

Symptoms of overdosage may include drowsiness, disorientation and extrapyramidal reactions. Anticholinergic or antiparkinson drugs or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. Symptoms are self-limiting and usually disappear within 24 hours.

Hemodialysis removes relatively little metoclopramide, probably because of the small amount of the drug in blood relative to tissues. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of drug. It is unlikely that dosage would need to be adjusted to compensate for losses through dialysis. Dialysis is not likely to be an effective method of drug removal in overdose situations.

Unintentional overdose due to misadministration has been reported in infants and children with the use of Reglan® syrup (Metoclopramide Oral Solution, USP). While there was no consistent pattern to the reports associated with these overdoses, events included seizures, extrapyramidal reactions, and lethargy.

Methemoglobinemia has occurred in premature and full-term neonates who were given overdoses of metoclopramide (1-4 mg/kg/day orally, intramuscularly or intravenously for 1-3 or more days). Methemoglobinemia has not been reported in neonates treated with 0.5 mg/kg/day in divided doses. Methemoglobinemia can be reversed by the intravenous administration of methylene blue.

DOSAGE AND ADMINISTRATION

For the Relief of Symptomatic Gastroesophageal Reflux

Administer from 10 mg to 15 mg Reglan® (Metoclopramide Hydrochloride, USP) orally up to q.i.d. 30 minutes before each meal and at bedtime, depending upon symptoms being treated and clinical response (see **CLINICAL PHARMACOLOGY** and **INDICATIONS AND USAGE**). If symptoms occur only intermittently or at specific times of the day, use of metoclopramide in single doses up to 20 mg prior to the provoking situation may be preferred rather than continuous treatment. Occasionally, patients (such as elderly patients) who are more sensitive to the therapeutic or adverse effects of metoclopramide will require only 5 mg per dose.

Experience with esophageal erosions and ulcerations is limited, but healing has thus far been documented in one controlled trial using q.i.d. therapy at 15 mg/dose, and this regimen should be used when lesions are present, so long as it is tolerated (see **ADVERSE REACTIONS**). Because of the poor correlation between symptoms and endoscopic appearance of the esophagus, therapy directed at esophageal lesions is best guided by endoscopic evaluation.

Therapy longer than 12 weeks has not been evaluated and cannot be recommended.

For the Relief of Symptoms Associated with Diabetic Gastroparesis (Diabetic Gastric Stasis)

Administer 10 mg of metoclopramide 30 minutes before each meal and at bedtime for two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation.

The initial route of administration should be determined by the severity of the presenting symptoms. If only the earliest manifestations of diabetic gastric stasis are present, oral administration of Reglan may be initiated. However, if severe symptoms are present, therapy should begin with Reglan Injectable (I.M. or I.V.). Doses of 10 mg may be administered slowly by the intravenous route over a 1- to 2-minute period.

Administration of Reglan Injectable (Metoclopramide Injection, USP) up to 10 days may be required before symptoms subside, at which time oral administration may be instituted. Since diabetic gastric stasis is frequently recurrent, Reglan therapy should be reinstituted at the earliest manifestation.

For the Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy

For doses in excess of 10 mg, Reglan Injectable should be diluted in 50 mL of a parenteral solution.

The preferred parenteral solution is Sodium Chloride Injection (normal saline), which when combined with Reglan Injectable, can be stored frozen for up to 4 weeks. Reglan Injectable is degraded when admixed and frozen with Dextrose-5% in Water. Reglan Injectable diluted in Sodium Chloride Injection, Dextrose-5% in Water, Dextrose-5% in 0.45% Sodium Chloride, Ringer's Injection, or Lactated Ringer's Injection may be stored up to 48 hours (without freezing) after preparation if protected from light. All dilutions may be stored unprotected from light under normal light conditions up to 24 hours after preparation.

Intravenous infusions should be made slowly over a period of not less than 15 minutes, 30 minutes before beginning cancer chemotherapy and repeated every 2 hours for two doses, then every 3 hours for three doses.

The initial two doses should be 2 mg/kg if highly emetogenic drugs such as cisplatin or dacarbazine are used alone or in combination. For less emetogenic regimens, 1 mg/kg per dose may be adequate.

If extrapyramidal symptoms should occur, inject 50 mg Benadryl® (diphenhydramine hydrochloride) intramuscularly, and EPS usually will subside.

For the Prevention of Postoperative Nausea and Vomiting

Reglan Injectable should be given intramuscularly near the end of surgery. The usual adult dose is 10 mg; however, doses of 20 mg may be used.

To Facilitate Small Bowel Intubation

If the tube has not passed the pylorus with conventional maneuvers in 10 minutes, a single dose (undiluted) may be administered slowly by the intravenous route over a 1- to 2-minute period.

The recommended single dose is: Pediatric patients above 14 years of age and adults—10 mg metoclopramide base. Pediatric patients (6-14 years of age)—2.5 to 5 mg metoclopramide base; (under 6 years of age)—0.1 mg/kg metoclopramide base.

To Aid in Radiological Examinations

In patients where delayed gastric emptying interferes with radiological examination of the stomach and/or small intestine, a single dose may be administered slowly by the intravenous route over a 1- to 2-minute period.

For dosage, see intubation above.

USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 mL/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

See **OVERDOSAGE** section for information regarding dialysis.

Metoclopramide undergoes minimal hepatic metabolism, except for simple conjugation. Its safe use has been described in patients with advanced liver disease whose renal function was normal.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

ADMIXTURE COMPATIBILITIES

Reglan Injectable (Metoclopramide Injection, USP) is compatible for mixing and injection with the following dosage forms to the extent indicated below:

Physically and Chemically Compatible Up to 48 Hours

Cimetidine Hydrochloride (SK&F), Mannitol, USP (Abbott), Potassium Acetate, USP (Invenex), Potassium Phosphate, USP (Invenex).

Physically Compatible Up to 48 Hours

Ascorbic Acid, USP (Abbott), Benztropine Mesylate, USP (MS&D), Cytarabine, USP (Upjohn), Dexamethasone Sodium Phosphate, USP (ESI, MS&D), Diphenhydramine Hydrochloride, USP (Parke-Davis), Doxorubicin Hydrochloride, USP (Adria), Heparin Sodium, USP (ESI), Hydrocortisone Sodium Phosphate (MS&D), Lidocaine Hydrochloride, USP (ESI), Multi-Vitamin Infusion (must be refrigerated-USV), Vitamin B Complex with Ascorbic Acid (Roche).

Physically Compatible Up to 24 Hours (*Do not use if precipitation occurs*)

Clindamycin Phosphate, USP (Upjohn), Cyclophosphamide, USP (Mead-Johnson), Insulin, USP (Lilly).

Conditionally Compatible (*Use within one hour after mixing or may be infused directly into the same running IV line*)

Ampicillin Sodium, USP (Bristol), Cisplatin (Bristol), Erythromycin Lactobionate, USP (Abbott), Methotrexate Sodium, USP (Lederle), Penicillin G Potassium, USP (Squibb), Tetracycline Hydrochloride, USP (Lederle).

Incompatible (*Do Not Mix*)

Cephalothin Sodium, USP (Lilly), Chloramphenicol Sodium, USP (Parke-Davis), Sodium Bicarbonate, USP (Abbott).

HOW SUPPLIED

Each white, capsule-shaped, scored Reglan® Tablet contains 10 mg metoclopramide base (as the monohydrochloride monohydrate). Available in bottles of 100 (NDC 0031-6701-63), and 500 tablets (NDC 0031-6701-70).

Each green, elliptical-shaped Reglan® Tablet (Metoclopramide Tablets, USP) contains 5 mg metoclopramide base (as the monohydrochloride monohydrate). Available in bottles of 100 tablets (NDC 0031-6705-63). **Dispense tablets in tight, light-resistant container.**

Reglan® Syrup, (Metoclopramide Oral Solution, USP) 5 mg metoclopramide base (as the monohydrochloride monohydrate) per 5 mL, available in pints (NDC 0031-6706-25). **Dispense syrup in tight, light-resistant container.**

PRESERVATIVE-FREE

Reglan® Injectable (Metoclopramide Injection, USP) 5 mg metoclopramide base (as the monohydrochloride monohydrate) per mL; available in 2 mL single dose vials in cartons of 25 (NDC 0031-6709-72), 10 mL single dose vials in cartons of 25 (NDC 0031-6709-78), 30 mL single dose vials in cartons of 25 (NDC 0031-6709-24), 2 mL ampuls in cartons of 25 (NDC 0031-6709-95).

Container	Total Contents #	Concentration #	Administration
2 mL single dose vial/ampul	10 mg	5 mg/mL	FOR IV or IM ADMINISTRATION
10 mL single dose vial	50 mg	5 mg/mL	FOR IV INFUSION ONLY; DILUTE BEFORE USING
30 mL single dose vial	150 mg	5 mg/mL	FOR IV INFUSION ONLY; DILUTE BEFORE USING

Metoclopramide base (as the monohydrochloride monohydrate)

Store vials and ampuls in carton until used. Do not store open single dose vials or ampuls for later use, as they contain no preservative.

This product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

Dilutions may be stored unprotected from light under normal light conditions up to 24 hours after preparation.

Tablets, Syrup and Injectable should be stored at controlled room temperature, between 20°C and 25°C (68°F and 77°F).

Reglan Injectable is manufactured for Pharmaceutical Division, A.H. Robins Company, Richmond, Virginia 23220 by Elkins-Sinn, Inc., Cherry Hill, NJ 08003, a subsidiary of A.H. Robins.